10622687 - 10.27.03

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 471/02, A61K 31/44, C07D 513/02 // (C07D 471/02, 221:00, 209:00, 209:00) (C07D 513/02, 333:00, 221:00, 209:00, 209:00)

A1

(11) International Publication Number: **WO 96/11929**

(43) International Publication Date: 25 April 1996 (25.04.96)

(21) International Application Number: PCT/EP95/03887

(22) International Filing Date: 2 October 1995 (02.10.95)

(30) Priority Data:
9420521.8 12 October 1994 (12.10.94) GB

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(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: BIHETEROARYL-CARBONYL AND CARBOXAMIDE DERIVATIVES WITH 5HT 2C/2B ANTAGONISTS ACTIVITY

(57) Abstract

The invention relates to indole and indoline compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of CNS disorders (5HT 2C/2B) antagonists.

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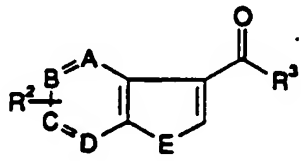
BIHETEROARYL-CARBONYL AND CARBOXAMIDE DERIVATIVES WITH 5HT 2C/2B ANTAGONISTS ACTIVITY

This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

WO 95/01976 (SmithKline Beecham plc) describes indoline derivatives which are described as possessing $5HT_{2C}$ receptor antagonist activity. A structurally distinct class of compounds has now been discovered, which have been found to have $5HT_{2C}$ receptor antagonist activity. Certain compounds of the invention also exhibit $5HT_{2B}$ antagonist activity. $5HT_{2C/2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Accordingly, in a first aspect, the present invention provides a compound of formula (I) or a salt, solvate or hydrate thereof:



(I)

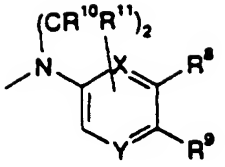
wherein:

A, B, C and D are all carbon atoms or one of A, B, C or D is nitrogen and the others are all carbon;

E is oxygen, sulphur, CH_2 or NR^1 where R^1 is hydrogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylthio, nitro, CF_3, cyano, NR^4R^5, $CONR^4R^5$, CO_2R^6 or OR^7 where R^4, R^5, R^6 and R^7 are as hydrogen or C_{1-6} alkyl; and

R^3 is a group of formula (i)



(i)

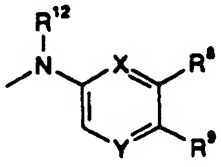
in which:

X and Y are both nitrogen, one is nitrogen and the other is carbon or a CH group or one is a CH group and the other is carbon or a CH group;

R^8 and R^9 groups are independently C_{1-6} alkyl optionally substituted by one or more halogen atoms, C_{2-6} alkenyl, C_{3-6}cycloalkyloxy, C_{3-6}cycloalkylC_{1-6}alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, C_{1-6} alkylthio, C_{3-6} cycloalkylthio, C_{3-6} cycloalkyl-C_{1-6} alkylthio, C_{1-6}alkoxy, hydroxy, halogen, nitro, CF_3, C_2F_5, OCF_3, SCF_3, SO_2CF_3, SO_2F, formyl, C_{2-6} alkanoyl, cyano, optionally substituted phenyl or thienyl, NR^4R^5, $CONR^4R^5$ or CO_2R^6 where R^4, R^5 and R^6 are as defined for R^1; or R^8 and R^9 form part of an optionally substituted 5-membered carbocyclic or heterocyclic ring; and

R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl;

or R^3 is a group of formula (ii):

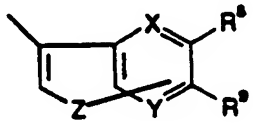


(ii)

in which R^8 and R^9 are as defined in formula (i), X and Y are both nitrogen, one is nitrogen and the other is a CH group or X and Y are both CH groups; and

R^{12} is hydrogen or C_{1-6} alkyl,

or R^3 is a group of formula (iii):



in which R^8, R^9, X and Y are as defined for formula (i) and Z is oxygen, sulphur, CH_2 or NR^{13} where R^{13} is hydrogen or C_{1-6} alkyl.

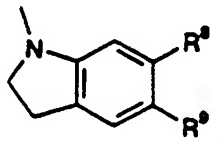
C_{1-6} alkyl moieties whether alone or as part of another group can be straight chain or branched.

Suitably A, B, C and D are all carbon atoms giving an indole ring, or one of A, B, C or D is nitrogen and the others are all carbon giving an azaindole ring, that is to say, a 4-, 5-, 6- or 7-azaindole ring. Preferably A, B and C are all carbon atoms and D is a nitrogen atom, giving a 7-azaindole ring, also known as a pyrrolo[2,3-b]pyridine ring

Preferably E is NR^1 where R^1 is hydrogen.

Preferably R^2 is hydrogen.

Preferably R^3 is a group of formula (i). Preferably X and Y form part of a phenyl ring, that is to say one of X or Y is carbon and the other is a CH group or both of X and Y are CH groups. Most preferably R^3 is an indoline ring, that is to say a group of formula (A):



(A)

in which R^8 and R^9 are as defined in formula (i).

When R^8 and R^9 form part of an aromatic ring suitable rings include thiophene, furan and pyrrole rings. Preferred R^8 and R^9 groups, which can be the same or different, include C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, halogen, CF_3, and CO_2R^6 where R^6 is hydrogen or C_{1-6} alkyl. Preferably R^8 is trifluoromethyl and R^9 is C_{1-6}alkylthio, for example methylthio.

Particularly preferred compounds of formula (I) include:

1-(3-Pyrrolo[2,3-b]pyridylcarbonyl)indoline,

5-Nitro-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,

5-Amino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,

5-Dimethylamino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,

5-Diethylamino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,

N-(1-Methyl-5-indolyl)pyrrolo[2,3-b]pyridine-3-carboxamide,

2,3-Dihydro-6-methyl-3-(3-pyrrolo[2,3-b]pyridylcarbonyl)-1*H*-pyrrolo[3,2-e]indole,

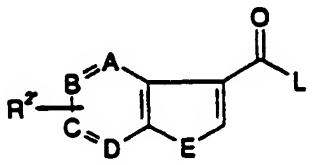
2,3-Dihydro-5-methyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,

N-(1-Methyl-5-indolyl)-1-methylpyrrolo[2,3-b]pyridine-3-carboxamide,

2,3-Dihydro-5-methyl-1-(1-methyl-3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-ethyl-1-(1-methyl-3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-pyrrolo[3,2-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-ethyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole
N-(1-Methyl-5-indolyl)pyrrolo[2,3-c]pyridine-3-carboxamide,
2,3-Dihydro-5-ethyl-1-(3-pyrrolo[2,3-c]pyridylcarbonyl)pyrrolo[2,3-f]indole
2,3-Dihydro-5-methyl-1-(3-indolylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(1-methyl-3-indolylcarbonyl)pyrrolo[2,3-f]indole
5-Methoxy-6-trifluoromethyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl) indoline
6-Chloro-5-methyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,
6,7-Dihydro-5-(3-pyrrolo[2,3-b]pyridylcarbonyl)-5H-thieno[2,3-f] indole,
or pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):



(II)

with a compound of formula (III):

$$X\text{-}R^{3'} \quad \text{(III)}$$

wherein A, B, C, and D are as defined in formula (I), E is as defined in formula (I) or is a group $NR^{1'}$, L is a leaving group and X is hydrogen or a metal atom, and the variables, $R^{1'}$, $R^{2'}$ and $R^{3'}$ are R^1, R^2 and R^3 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$ and $R^{3'}$ when other than R^1, R^2 and R^3 respectively to R^1, R^2 and R^3, interconverting R^1, R^2 and R^3 and forming a pharmaceutically acceptable salt thereof.

Suitably L is a leaving group such as halogen, in particular chloro.

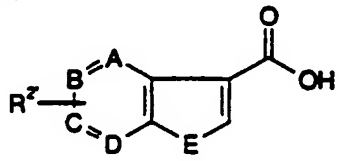
Suitably X is hydrogen or a metal atom such as lithium or magnesium.

Interconversion of a compound of formula (I) into another compound of formula (I) is carried out by conventional procedures well known in the art.

For example, in the case wherein R^1 is hydrogen, it is possible to introduce a C_{1-6}alkyl group by conventional alkylation using 1 molar equivalent of a C_{1-6}alkyl halide and 1 molar equivalent of a suitable base in an inert solvent.

It should be appreciated that it may be necessary to protect certain reactive groups during coupling reaction (a) above. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Compounds of formula (II) are known compounds or can be prepared from compounds of formula (IV):



(IV)

in which $R^{2'}$, A, B, C, D and E are as defined in formula (II) using standard procedures.

Compounds of formula (III) can be prepared according to the procedures outlined in WO 95/01976. Compounds of formula (IV) are commercially available or can be prepared using standard procedures.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2B/2C}$ receptor antagonist activity and are believed to be of potential use fo the treatment or prophylasis of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtrati n. The compound can be sterilised by exposure t ethylene

oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg; and such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Description 1
N-Acetyl-5-nitroindoline (D1)

A solution of 5-nitroindoline (12 g) in acetic anhydride (150 ml) was treated with pyridine (2 ml). The solution was then heated under reflux for 1 h, cooled and the excess acetic anhydride removed by evaporation *in vacuo*. On addition of water (150 ml), the title compound precipitated as a tan solid (13 g, 86%): ^{1}H NMR δ ($CD_3OD/CDCl_3$) 2.29 (3H, s), 3.29 (2H, t, J = 8 Hz), 4.20 (2H, t, J = 8 Hz), 8.04 (1H, s), 8.13 (1H, dd, J = 2, 9 Hz) and 8.3 (1H, d, J = 9 Hz).

Description 2
5-Dimethylaminoindoline (D2)

A suspension of N-acetyl-5-nitroindoline (D1) (10 g), 37% aqueous formaldehyde (10 ml), and 5% Pd/C (1.5 g) in ethanol (200 ml) was hydrogenated at a pressure of 45 psi for 18 h. The mixture was then filtered through Kieselguhr, and evaporated to dryness to afford crude N-acetyl-5-dimethylaminoindoline as a white solid. This was dissolved in conc. HCl (6 ml) and heated over a steambath for 45 minutes. The solution was then basified by dropwise addition of aqueous K_2CO_3 and extracted with chloroform(3x20 ml). The organic fraction was dried ($MgSO_4$) and evaporated *in vacuo* to give an oil. Purification by flash chromatography, eluting with 5% methanol/chloroform gave the title compound as an oil (3.4 g, 86%): ^{1}H NMR δ ($CD_3OD/CDCl_3$) 2.8 (6H, s), 3.0 (3H, t, J = 8 Hz), 3.51 (2H, t, J = 8 Hz), 6.61 (2H, m) and 6.75 (1H, br s).

Description 3
5-Diethylaminoindoline (D3)

A suspension of N-acetyl-5-nitroindoline (D1) (4 g), excess acetaldehyde (20 ml) and 5% Pd/C (0.5 g) in ethanol (150 ml) was hydrogenated at a pressure of 45 psi for 18 h. The mixture was then filtered through Kieselguhr, and evaporated to dryness to afford crude N-acetyl-5-diethylaminoindoline as a white solid (4.3 g). This was dissolved in conc. HCl (5 ml) and heated over a steambath for 0.5 h. The solution was then basified by dropwise addition of aqueous K_2CO_3 and extracted with chloroform(3 x 20 ml). The organic fraction was dried ($MgSO_4$) and evaporated *in vacuo* to give an oil. Purification by flash chromatography, eluting with 5% methanol/chloroform gave the title compound as an oil (3 g, 86%): ^{1}H NMR δ ($CD_3OD/CDCl_3$) 1.08 (6H, t, J = 8

Hz), 3.0 (2H, t, J = 8 Hz), 3.19 (4H, q, J = 7, 14 Hz), 3.52 (2H, t, J = 8 Hz), 6.53 (1H, dd, J = 2, 8 Hz), 6.6 (1H, d, 8 Hz) and 6.71 (1H, br s).

Description 4

1-Methyl-pyrrolo[2,3-b]pyridine-3-carboxylic acid (D4)

A solution of 1-methyl-pyrrolo[2,3-b]pyridine (2.82 g, 21 mmol) and hexamethylenetetramine (4.41 g, 32 mmol) in acetic acid (8.4 ml) and water (17.7 ml) was heated under reflux for 6 h. Water (150 ml) was added and the mixture was extracted with ether. The extracts were washed with water and brine, then dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography eluting with ether gave 1-methylpyrrolo[2,3-b]pyridine-3-carboxaldehyde (900 mg, 27%).

A solution of this aldehyde (560 mg, 3.5 mmol) in acetone (20 ml) and sodium carbonate (371 mg, 3.5 mmol) in water (2 ml) was treated over 20 min with a solution of potassium permanganate (1.1 g, 7 mmol) in water (40 ml). Further quantities (2 x 300 mg) of potassium permanganate were added after 30 and 60 min. The mixture was filtered and the solution was evaporated to dryness. The residue was triturated with 50% methanol/ethyl acetate, the resulting solution was evaporated to dryness and the residual solid was triturated with 5% methanol/ethyl acetate to give the title compound as a white solid (390 mg, 63%). Flash chromatography of a sample eluting with 10% ethanol/chloroform gave the title compound: mp 249-251 °C; ^{1}H NMR δ (d_6DMSO) 3.87 (1H, s), 7.26 (1H, dd, J = 5, 8 Hz), 8.24 (1H, s), 8.30 (2H, m) and 12.25 (1H, br s); Found C, 59.81; H, 4.80; N, 15.62; $C_9H_8N_2O_2.0.75\ H_2O$ requires C, 59.82; H, 4.74; N,15.51%.

Description 5

2-Nitro-2-pyridylacetic acid, ethyl ester (D5)

Ethyl acetoacetate (6.37 ml, 50 mmol) was added dropwise to a stirred suspension of 80% sodium hydride (1.5 g, 50 mmol) in dry DMF (20 ml), keeping the temperature below 50 °C. After 30 min 2-chloro-3-nitropyridine (3.96 g, 25 mmol) was added in portions. The mixture was stirred at room temperature for 90 min and at 70 °C for 1 h, then concentrated *in vacuo*. The residue was diluted with water (150 ml), acidified (HOAc) and extracted with ether. The extracts were washed with water and brine, then dried (Na_2SO_4) and evaporated t leave an orange oil (6.7 ml).

This crude product was dissolved in dry ether (80 ml), made acidic with 1N ethereal HCl and stirred at room temperature overnight. The precipitated solid was filtered off and washed with dry ether to give the HCl salt of the title compound as a pal yellow solid (4.3 g, 70%). The free base was obtained by treating an aqueous solution of the product with 10% sodium carbonate, then extracting with ethyl acetate. After drying (Na_2SO_4) and evaporating the extracts, the title compound was obtained as a yellow oil (3.38 g): ^{1}H NMR δ ($CDCl_3$) 1.26 (3H, t, J = 7 Hz), 4.20 (2H, q, J = 7 Hz), 4.34 (2H, s), 7.49 (1H, dd, J = 5, 8 Hz), 8.43 (1H, d, J = 8 Hz) and 8.80 (1H, d, J = 5 Hz).

Description 6
Ethyl α-(3-nitro-2-pyridyl)-β-dimethylaminoacrylate (D6)

A solution of dimethylformamide diethyl acetal (1.3 ml, 7.5 mmol) in dry DMF (5 ml) was added to a stirred solution of 2-nitro-2-pyridylacetic acid, ethyl ester (D5) (1 g, 4.8 mmol) in DMF (20 ml) to give a red solution which was heated at 70 °C overnight. The solution was evaporated *in vacuo* and the residue was extracted repeatedly with boiling hexane. On cooling the title compound separated as red crystals (545 mg, 43%): mp 135-138 °C ; ^{1}H NMR δ ($CDCl_3$) 1.14 (3H, t, J = 7 Hz), 2.86 (6H, br s), 4.07 (2H, br s), 7.28 (1H, dd, J = 5, 8 Hz), 7.78 (1H, s), 8.19 (1H, d, J = 8 Hz) and 8.76 (1H, d, J = 5 Hz); Found C, 54.40; H, 5.68; N, 15.76; $C_{12}H_{15}N_3O_4$ requires C, 54.33; H, 5.70; N, 15.84%.

Description 7
Ethyl pyrrolo[3,2-b]pyridyl-3-carboxylate (D7)

A suspension of ethyl α-(3-nitro-2-pyridyl)-β-dimethylaminoacrylate (D6) (0.5 g, 1.9 mmol) in ethanol (150 ml) was hydrogenated over 10% Pd/C at atmospheric pressure for 24 h. The catalyst was filtered off and the solvent was evaporated. The residual solid was chromatographed, eluting with 5% ethanol/ethyl acetate, to give the title compound (250 mg, 70%): mp 213-216 °C (EtOAc); ^{1}H NMR δ (d_6DMSO) 1.31 (3H, t, J = 7 Hz), 4.27 (2H, d, J = 7 Hz), 7.20 (1H, dd, J = 5, 8 Hz), 7.85 (1H, d, J = 8 Hz), 8.30 (1H, s), 8.48 (1H, d, J = 5 Hz) and 12.1 (1H, br s); Found C, 63.05; H, 5.34; N, 14.73; $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.30; N, 14.73%.

Description 8

1-Methoxy-4-nitro-2-trifluoromethylbenzene (D8)

Sodium (11.78g, 0.512 mol) was dissolved in dry methanol (1 l) and to the resulting solution was added a solution of 1-chloro-4-nitro-2-trifluoromethyl-benzene (96.22g, 0.427 mol) in methanol (100 ml). The reaction mixture was refluxed for 3 h then cooled and evaporated *in vacuo*. The residue was partitioned between water (500 ml) and dichloromethane (3 x 400 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the title compound (93.76g, 99%) as a white solid.

NMR ($CDCl_3$) δ: 4.05 (3H, s), 7.12 (1H, d), 8.45 (1H, dd), 8.52 (1H, d).

Description 9

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D9)

A mixture of 1-methoxy-4-nitro 2-trifluoromethylbenzene (D8) (93g, 0.421 mol) and 4-chlorophenoxyacetonitrile (77.55g, 0.463 mol) in dry DMF (500 ml) was added dropwise over 0.75 h to a stirred solution of KO^tBu (103.85g, 0.927 mol) in dry DMF (400 ml) at -10° C. After complete addition the resulting purple solution was maintained at -10° C for 1 h then poured into a mixture of ice/water (1.5 l) and 5 M aqueous HCl (1.5 l). The resulting mixture was extracted with dichloromethane (3 x 1 l). The combined extracts were washed with water (3 l), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica using 10-40% ethyl acetate/petroleum ether as eluant to give the crude product which was recrystallised from ethyl acetate/petroleum ether to afford the title compound (85.13g, 78%) as a white solid. Mp 103-104 °C.

NMR ($CDCl_3$) δ: 4.10 (3H, s), 4.37 (2H, s), 7.34 (1H, s), 8.53 (1H, s).

Description 10

5-Methoxy-6-trifluoromethylindole (D10)

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D9) (85g, 0.327 mol) in ethanol/water (9:1, 1.6 l) and glacial acetic acid (16 ml) was hydrogenated over 10% palladium on carbon (50 g) at 50 psi for 0.5 h at room temperature. The reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between aqueous K_2CO_3 (1 l) and dichloromethane (2 x 1 l) and the combined organic extract was dried (Na_2SO_4) and evaporated to afford the title indole (67.63g, 96%) as a grey solid.

NMR ($CDCl_3$) δ: 3.94 (3H, s), 6.53 (1H, m), 7.21 (1H, s), 7.32 (1H, m), 7.64 (1H, s), 8.25 (1H, br s).

Description 11
5-Methoxy-6-trifluoromethylindoline (D11)

The indole (D10) (67.63g, 0.315 mol) was treated with sodium cyanoborohydride (40 g, 0.637 mol) in glacial acetic acid (500 ml) using standard methodology to afford the title indoline (67.73g, 99%) as an off-white solid.

NMR ($CDCl_3$) δ: 3.07 (2H, t), 3.58 (2H, t), 3.67 (1H, br s), 3.83 (3H, s), 6.83 (1H, s), 6.88 (1H, s).

Example 1
1-(3-Pyrrolo[2,3-b]pyridylcarbonyl)indoline (E1)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (103 mg, 0.635 mmol) in thionyl chloride (5 ml) was heated under reflux for 2 h, then cooled and the excess thionyl chloride evaporated *in vacuo*. The residue in dichloromethane (10 ml) was added in portions to a solution of indoline (76 mg, 0.635 mmol) and triethylamine (193 mg, 1.9 mmol) in dichloromethane (20 ml). The mixture was heated under reflux for 4 h, cooled and diluted with chloroform (20 ml). The solution was washed with water, then dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography, eluting with 10% methanol in chloroform gave the title compound (30 mg,18%): mp 257-260 °C; ^1H NMR δ (CD_3OD) 3.23 (2H, t, J = 10 Hz), 4.42 (2H, t, J = 10 Hz), 7.05 (1H, t, J = 10 Hz), 7.1-7.35 (3H, m), 7.92 (1H, d, J = 8 Hz), 7.99 (1H, s), 8.32 (1H, dd, J = 6, 2 Hz) and 8.4 (1H, dd, J = 2, 8 Hz); Found C, 72.75; H, 5.10; N, 15.89, $C_{16}H_{13}N_3O$ requires C, 72.99; H, 4.98; N, 15.96%.

Example 2
5-Nitro-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline (E2)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (1.51 g, 9.3 mmol) in thionyl chloride (20 ml) was heated under reflux for 4 h, then cooled and the excess thionyl chloride evaporated *in vacuo*. The residue in dichloromethane (150 ml) was added in portions to a solution of 5-nitroindoline (1.37 g, 8.4 mmol) and triethylamine

(0.94 g, 27.9 mmol) in dichloromethane (20 ml). The mixture was heated under reflux overnight, cooled and diluted with chloroform (100 ml). The solution was washed with water, then dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography, eluting with 10% methanol in chloroform gave the title compound (0.83 g, 32%): mp 320-322 °C; ^1H NMR δ (CD_3OD) 3.3 (2H, overlapping with solvent peak), 4.42 (2H, t, J = 8 Hz), 7.25 (1H, dd, J = 3, 8 Hz), 8.1-8.35 (6H, m), and 8.45 (1H, dd, J = 1.5, 8 Hz); Found C, 59.44; H, 4.01; N, 16.80; $C_{16}H_{12}N_4O_3.H_2O$ requires C, 58.89; H, 4.32; N, 17.16%.

Example 3

5-Amino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline (E3)

A suspension of 5-nitro-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline (E2) (100 mg) in ethanol (20 ml) was treated with 5% Pd/C (20 mg). The suspension was hydrogenated at 50 psi overnight, then filtered through celite and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography eluting with 5% and then 10% ethanol in chloroform to give the title compound as a solid (34mg, 38%): ^1H NMR δ ($CD_3OD/CDCl_3$) 3.13 (2H, t, J = 8 Hz), 4.32 (2H, t, J = 8 Hz), 6.58 (1H, br d), 6.67 (1H, s), 7.22 (1H, dd, J = 5, 8 Hz), 7.75 (2H, s), 8.3 (1H, dd, J = 1, 5 Hz) and 8.9 (1H, br d); Found C, 65.64; H, 5.09; N, 18.99; $C_{16}H_{14}N_4O.\ 0.75H_2O$ requires C, 65.85; H, 5.35; N, 19.19%.

Example 4

5-Dimethylamino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline (E4)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (306 mg, 1.88 mmol) in thionyl chloride (10 ml) was stirred for 18 h at room temperature. Excess thionyl chloride was evaporated *in vacuo* and the residue dissolved in chloroform was added in portions to a solution of 5-dimethylamino-indoline (305 mg, 1.88 mmol) and triethylamine (570 mg, 5.6 mmol) in chloroform (20 ml). The mixture was heated at 50 °C for 18 h cooled and diluted with chloroform (20 ml). The solution was washed with water, then dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography, eluting with 10% ethanol /dichloromethane gave the title compound (21 mg, 21%): ^1H NMR δ (CD_3OD) 2.93 (6H, s), 3.15 (2H, t, J = 8 Hz), 4.3 (2H, t, J = 8 Hz), 6.58 (1H, br d, J = 9 Hz) 6.69 (1H, s), 7.16 (1H, m), 7.72 (1H, s) 7.88 (1H, br s), 8.36(1H, d, J = 4 Hz) and 8.42(1H, br d, 9 Hz); Found C, 69.73; H, 6.01; N, 17.87; $C_{18}H_{18}N_4O.\ 0.25H_2O$ requires C, 69.55; H, 5.99; N, 18.02%.

Example 5

5-Diethylamino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline (E5)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (200 mg, 1.23 mmol) in thionyl chloride (10 ml) was stirred for 18 h at room temperature. Excess thionyl chloride was evaporated *in vacuo* and the residue dissolved in dichloromethane was added in portions to a solution of 5-diethylamino-indoline (235 mg, 123 mmol) and triethylamine (374 mg, 3.74 mmol) in dichloromethane. The mixture was heated at 50 °C for 18 h cooled and the solvent evaporated *in vacuo*. Flash chromatography, eluting with 5% and then 10% ethanol /dichloromethane gave the title compound as a white solid (108 mg, 26%): mp 221-223 °C. ^{1}H NMR δ (CD_3OD/CD_3Cl) 1.08 (6H, t, *J* 0= 7). 3.0 (2H, t, *J* = 8 Hz), 3.19 (4H, q, *J* = 7, 14 Hz), 4.35 (2H, t, *J* = 8 Hz), 6.50 (1H, dd, *J* = 2, 8 Hz), 6.63 (1H, s), 7.18(1H, dd, *J* = 4, 8 Hz), 7.9 (1H, br d), 8.08 (1H, d, *J* = 2 Hz), 8.3 (1H, m) and 8.39(1H, d, *J* = 8 Hz); Found C, 70.87; H, 6.41; N, 16.50; $C_{20}H_{22}N_4O$. $0.25H_2O$ requires C, 70.88; H, 6.56; N, 16.53%.

Example 6

***N*-(1-Methyl-5-indolyl)pyrrolo[2,3-b]pyridine-3-carboxamide (E6)**

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid[1] (162 mg, 1 mmol) in thionyl chloride (2 ml) was heated under reflux for 2 h then kept at room temperature overnight. The mixture was evaporated to dryness, then a suspension of the residue in dichloromethane (10 ml) was added in portions to a solution of 1-methyl-5-aminoindole (146 mg, 1 mmol) and triethylamine (0.28 ml, 2 mmol) in dichloromethane (10 ml). After 2 h the mixture was washed with 10% sodium carbonate solution and brine, then was dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography, eluting with ethyl acetate gave the title compound (138 mg, 48%): mp 250-253 °C; ^{1}H NMR δ (d_6DMSO) 3.78 (3H, s), 6.41 (1H, d, *J* = 4 Hz), 7.23 (1H, dd, *J* = 8, 4 Hz),7.32 (1H, d, *J* = 4 Hz), 7.44 (2H, m), 8.0 (1H, s), 8.32 (1H, d, *J* = 4 Hz), 8.53 (1H, d, *J* = 8 Hz) 9.7 (1H, s) and 12.2 (1H, s); Found C, 69.95; H, 5.10; N, 18.89; $C_{17}H_{14}N_4O$ requires C, 70.33; H, 4.86; N, 19.30%.

[1]Robison, M. M. and Robison, B. L. *J. Am Chem. Soc.*, 1956, *78*, 1247

Example 7

2,3-Dihydro-6-methyl-3-(3-pyrrolo[2,3-b]pyridylcarbonyl)-1*H*-pyrrolo[3,2-e]indole (E7)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (162 mg, 1 mmol) in thionyl chloride (4 ml) was heated under reflux for 30 min. The mixture was evaporated *in vacuo* and the residue was added in portions as a suspension in dichloromethane (10 ml) to a solution of 2,3-dihydro-6-methyl-1*H*-pyrrolo[3,2-e]indole hydrochloride (208 mg, 1 mmol) and triethylamine (0.42 ml, 3 mmol) in dichloromethane (10 ml). After 2 h the dark green solution was washed with water and brine, then dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography of the residue, eluting with ethyl acetate gave the title compound (87 mg, 28%): mp 238-245 °C; ^{1}H NMR δ (d_6DMSO) 3.3 (2H, m), 3.8 (3H, s), 4.48 (2H, t, J = 8 Hz), 6.36 (1H, d, J = 4 Hz), 7.2 (1H, dd, J = 8, 4 Hz), 7.28 (1H, d, J = 9 Hz), 7.36 (1H, d, J = 4 Hz), 8.05 (1H, br d, J = 9 Hz), 8.13 (1H, s), 8.32 (1H, d, J = 4 Hz), 8.42 (1H, d, J = 8 Hz) and 12.3 (1H, br s); Found C, 71.16; H, 5.23; N, 17.42; $C_{19}H_{16}N_4O$. 0.25 H_2O requires C, 71.12; H, 5.18; N, 17.46%.

Example 8

2,3-Dihydro-5-methyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole (E8)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (D1) (154 mg, 0.95 mmol) in thionyl chloride (3 ml) was heated under reflux for 2 h. The mixture was evaporated *in vacuo* and the residue was added in portions as a suspension in dichloromethane (10 ml) to a solution of 2,3-dihydro-5-methylpyrrolo[2,3-f]indole (120 mg, 0.7 mmol) and triethylamine (0.29 ml, 2.1 mmol) in dichloromethane (20 ml). After 2 h the dark green solution was washed with water and brine, then dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography of the residue, eluting with ethyl acetate gave the title compound (40 mg, 14%): mp 266-272 °C; ^{1}H NMR δ (d_6DMSO) 3.24 (2H, t, J = 8 Hz), 3.76 (3H, s), 4.44 (2H, t, J = 8 Hz), 6.37 (1H, d, J = 3 Hz), 7.22 (2H, m), 7.30 (1H, s), 8.11 (1H, d, J = 2 Hz), 8.31 (1H, d, J = 3 Hz), 8.42 (1H, d, J = 8 Hz) and 12.30 (1H, s); Found C, 72.42; H, 5.31; N, 17.70; $C_{19}H_{16}N_4O$ requires C, 72.14; H, 5.10; N, 17.71%.

Example 9

***N*-(1-Methyl-5-indolyl)-1-methylpyrrolo[2,3-b]pyridine-3-carboxamide (E9)**

A solution of 1-methylpyrrolo[2,3-b]pyridine-3-carboxylic acid (50 mg, 0.28 mmol) in thionyl chloride (1.5 ml) was stirred at room temperature overnight. The mixture was evaporated to dryness, then a suspension of the residue in dichloromethane (5 ml) was added in portions to a solution of 1-methyl-5-aminoindole (45 mg, 0.31 mmol) and triethylamine (0.12 ml, 0.86 mmol) in dichloromethane (10 ml). After 1 h the mixture was evaporated *in vacuo*. Flash chromatography, eluting with ethyl acetate gave the title compound (73 mg, 86%): mp 183-185 °C (EtOAc); ^{1}H NMR δ (d_6DMSO) 3.78 (3H, s), 3.92 (3H, s), 6.39 (1H, d, J = 3 Hz), 7.25 (2H, m), 7.42 (2H, m), 8.00 (1H, d, J = 1 Hz), 8.36 (1H, dd, J = 5, 1.5 Hz), 8.44 (1H, s), 8.52 (1H, dd, J = 8, 1.5 Hz) and 9.75 (1H, s); Found C, 69.70; H, 5.36; N, 18.05; $C_{18}H_{16}N_4O$. 0.25H_2O requires C, 70.00; H, 5.39; N, 18.14%.

Example 10

2,3-Dihydro-5-methyl-1-(1-methyl-3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole (E10)

A mixture of crude 1-methylpyrrolo[2,3-b]pyridine-3-carboxylic acid (176 mg, 1 mmol) in thionyl chloride (3 ml) was stirred at room temperature overnight.. The reagent was evaporated *in vacuo* and the residue was added in portions as a suspension in dichloromethane (10 ml) to a solution of 2,3-dihydro-5-methylpyrrolo[2,3-f]indole (172 mg, 1 mmol) and triethylamine (0.42 ml, 3 mmol) in dichloromethane (10 ml). After 1 h the solution was evaporated *in vacuo*. Flash chromatography of the residue, eluting with ethyl acetate gave the title compound (137 mg, 41%): mp 214-225 °C; ^{1}H NMR δ (d_6DMSO) 3.26 (2H, t, J = 7 Hz), 3.76 (3H, s), 3.91 (3H, s), 4.45 (2H, d, J = 7 Hz), 6.38 (1H, d, J = 3 Hz), 7.25 (2H, m), 7.33 (1H, s), 8.27 (1H, s), 8.32 (1H, s), 8.48 (1H, d, J = 3 Hz) and 7.97 (1H, d, J = 6 Hz); M^+ (Found) 330.147186; $C_{20}H_{18}N_4O$ requires 330.148061.

Example 11

2,3-Dihydro-5-ethyl-1-(1-methyl-3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole (E11)

A mixture of crude 1-methylpyrrolo[2,3-b]pyridine-3-carboxylic acid (260 mg, 1.5 mmol) in thionyl chloride (4 ml) was stirred at room temperature overnight. The

reagent was evaporated *in vacuo* and the residue was added in portions as a suspension in dichloromethane (10 ml) to a solution of 2,3-dihydro-5-ethylpyrrolo[2,3-f]indole (280 mg, 1.5 mmol) and triethylamine (0.63 ml, 4.5 mmol) in dichloromethane (25 ml). After 2 h the solution was evaporated *in vacuo*. Flash chromatography of the residue, eluting with ethyl acetate, followed by trituration with ether gave the title compound (165 mg, 32%): mp 210-213 °C; ^{1}H NMR δ ($CDCl_3$) 1.48 (3H, t, J = 7 Hz), 3.30 (2H, t, J = 7 Hz), 3.95 (3H, s), 4.15 (2H, q, J = 7 Hz), 4.40 (2H, t, J = 7 Hz), 6.46 (1H, d, J = 3 Hz), 7.08 (1H, d, J = 3 Hz), 7.18 (2H, m), 7.53 (1H, s), 8.20 (1H, br s) and 8.40 (2H, m); Found C, 73.13; H, 5.89; N, 16.11, $C_{21}H_{20}N_4O$ requires C, 73.23; H, 5.85; N,16.27%.

Example 12

2,3-Dihydro-5-methyl-1-(3-pyrrolo[3,2-b]pyridylcarbonyl)pyrrolo[2,3-f]indole (E12)

A solution of ethyl pyrrolo[3,2-b]pyridyl-3-carboxylate (D4) (260 mg, 1.37 mmol) and 2,3-dihydro-5-methylpyrrolo[2,3-f]indole (353 mg, 2.05 mmol) in xylene (20 ml) were heated under reflux for 48 h. The mixture was cooled, filtered, and washed with hexane. The resulting white solid was boiled in methanol (15 ml), cooled and filtered to give the title compound (310 mg, 72%): mp 338-342 °C; ^{1}H NMR δ ($CDCl_3$) 3.27 (2H, d, J = 7 Hz), 3.79 (3H, s), 4.4 (2H, m), 6.4 (1H, br s), 7.03 (1H, d, J = 3 Hz), 7.21 (1H, s), 7.25 (1H, m), 7.90 (1H, d, J = 8 Hz), 7.93 (1H, s) and 8.42 (1H, d, J = 3 Hz).

Example 13

2,3-Dihydro-5-ethyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole (E13)

A solution of pyrrolo[2,3-b]pyridine-3-carboxylic acid (D1) (200 mg, 1.20 mmol) in thionyl chloride (20 ml) was stirred at room temperature overnight. The mixture was evaporated to dryness and the residue was added in portions to a solution of 2,3-dihydro-5-ethylpyrrolo[2,3-f]indole (230 mg, 1.20 mmol) and triethylamine (0.61 ml, 4.2 mmol) in dichloromethane (20 ml). After 2 h the dark purple solution was washed with water and brine, then dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in methanol and stirred overnight with activated charcoal, filtered and solvent removed *in vacuo*. Flash chromatography of the residue, eluting with ethyl acetate, gave the title compound (130 mg, 33 %): mp 255-258 °C; ^{1}H NMR δ ($CDCl_3$) 1.46 (3H, t, J = 7 Hz), 3.29 (2H, t, J = 8 Hz), 4.12 (2H, q, J = 7 Hz), 4.41 (2H, t, J = 7 Hz), 6.42 (1H, d, J = 2 Hz), 7.05 (1H, d, J = 3 Hz), 7.20 (3H, m), 7.80 (1H, s), 8.40 (1H, d, J = 5 Hz), 8.50 (1H, d, J = 7 Hz) and 11.22 (1H, s); Found C, 72.30; H, 5.62; N, 16.67; $C_{20}H_{18}N_4O$ requires C, 72.71; H, 5.49; N, 16.96%.

Example 14

***N*-(1-Methyl-5-indolyl)pyrrolo[2,3-c]pyridine-3-carboxamide (E14)**

A suspension of pyrrolo[2,3-c]pyridine-3-carboxylic acid[1] (118 mg, 0.73 mmol) in thionyl chloride (5 ml) was heated under reflux overnight at room temperature. The mixture was evaporated to dryness, then a suspension of the residue in dichloromethane (5 ml) was added in portions to a solution of 1-methyl-5-aminoindole (106 mg, 0.73 mmol) and triethylamine (221 mg, 2.2 mmol) in dichloromethane (10 ml). The suspension was heated under reflux for 4 h, then washed with water (2 x 10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to afford an oil. Flash chromatography, eluting with 5% methanol in chloroform gave the title compound (25 mg, 12%): mp 295-297 °C; ^1H NMR δ ($CDCl_3/CD_3OD$) 3.8 (3H, s), 6.42 (1H, d, J = 4 Hz), 7.15 (1H, d, J = 4 Hz), 7.32 (2H, m, J = 4 Hz), 7.84 (1H, s), 8.2 (2H, s), 8.33 (1H, br s), 8.7 (1H, br s); Found C, 69.38; H, 4.85; N, 18.72; $C_{17}H_{14}N_4O.0.25\ H_2O$ requires C, 69.26; H, 4.87; N, 19.00%.

[1]Prokopov, A. A. and Yakhontov, L. N. *Khim. Geterotsikl. Soedin.*, 1978, 496

Example 15

2,3-Dihydro-5-ethyl-1-(3-pyrrolo[2,3-c]pyridylcarbonyl)pyrrolo[2,3-f]indole (E15)

A mixture of crude pyrrolo[2,3-c]pyridine-3-carboxylic acid (209 mg, 1.47 mmol) in thionyl chloride (10 ml) was stirred at room temperature overnight. The reagent was evaporated *in vacuo* and the residue was added in portions as a suspension in dichloromethane (5 ml) to a solution of 2,3-dihydro-5-ethylpyrrolo[2,3-f]indole (291 mg, 2.94 mmol) and triethylamine (296 mg, 2.94 mmol) in dichloromethane (5 ml). After 2 h the solution was evaporated *in vacuo*. Flash chromatography of the residue, eluting with 10% ethanol in chloroform, followed by trituration with ether gave the title compound (90 mg, 19%): mp 287-290 °C; ^1H NMR δ ($CDCl_3/CD_3OD$), 1.48 (3H, t, J = 7 Hz), 3.30 (2H, t, J = 7 Hz), 4.15 (2H, q, J =15, 7 Hz), 4.38 (2H, t, J = 7 Hz), , 6.4 (1H, br s), 7.08 (1H, d, J = 3 Hz), 7.22 (1H, s), 7.9 (2H, br s), 8.22 (1H, d, J = 7 Hz) and 8.75 (1H, s).

Example 16

2,3-Dihydro-5-methyl-1-(3-indolylcarbonyl)pyrrolo[2,3-f]indole (E16)

A solution of indole-3-carboxylic acid (150 mg, 0.93 mmol) and oxalyl chloride (0.1 ml) in dicloromethane (20 ml) was stirred at room temperature overnight. The mixture was evaporated to dryness and the residue was added in portions to a solution of 2,3-dihydro-5-methylpyrrolo[2,3-f]indole (160 mg, 0.93 mmol) and triethylamine (0.47 ml, 3.2 mmol) in dichloromethane (20 ml). After 2 h the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography, eluting with ethyl acetate, to give the title compound (220 mg, 75 %): mp 279-282 °C; ^{1}H NMR δ (d_6DMSO) 3.25 (2H, t, J = 7 Hz), 3.77 (3H, s), 4.41 (2H, t, J = 7 Hz), 6.37 (1H, d, J = 2 Hz), 7.08 - 7.24 (3H, m), 7.33 (1H, s), 7.49 (1H, d, J = 7 Hz), 7.98 (1H, d, J = 2 Hz), 8.05 (1H, d, J = 7 Hz), 8.30 (1H, s); Found C, 74.09; H, 5.60; N, 12.60; $C_{20}H_{17}N_3O.0.5H_2O$ requires C, 74.05; H, 5.59; N, 12.95%.

Example 17

2,3-Dihydro-5-methyl-1-(1-methyl-3-indolylcarbonyl)pyrrolo[2,3-f]indole (E17)

A solution of 1-methylindole-3-carboxylic acid (160 mg, 0.93 mmol) and oxalyl chloride (0.1 ml) in dicloromethane (20 ml) was stirred at room temperature overnight. The mixture was evaporated to dryness and the residue was added in portions to a solution of 2,3-dihydro-5-methylpyrrolo[2,3-f]indole (160 mg, 0.93 mmol) and triethylamine (0.47 ml, 3.2 mmol) in dichloromethane (20 ml). After 2 h the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography, eluting with ethyl acetate, to give the title compound (200 mg, 65 %): mp 242-244 °C; ^{1}H NMR δ (d_6DMSO) 3.25 (2H, t, J = 7 Hz), 3.75 (3H, s), 3.88 (3H, s), 4.40 (2H, t, J = 7 Hz), 6.35 (1H, d, J = 2 Hz), 7.12 - 7.32 (4H, m), 7.52 (1H, d, J = 7 Hz), 8.03 (1H, s), 8.07 (1H, d, J = 7 Hz) and 8.30 (1H, s).

Example 18

5-Methoxy-6-trifluoromethyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl) indoline (E18)

To a suspension of pyrrolo [2,3-b] pyridine-3-carboxylic acid (0.16g, 1 mmol) in dry tetrahydrofuran (10 ml) was added oxalyl chloride (85 mL, 1 mmol) and N,N-dimethylformamide (1 drop). After stirring at room temperature for 1 h, a solution of 5-methoxy-6-trifluoromethyl indoline (D11) (0.22g, 1 mmol) and triethylamine (0.19 mL, 2 mmol) in dry tetrahydrofuran (5 mL) was added. The mixture was stirred for 4 h, then

poured into water. The precipitate was filtered off, washed with water and dried. The crude product was recrystallised from dichloromethane/methanol to give the title compound (0.10g, 28%), mp. >250°C.

NMR (d_6DMSO) δ: 3.28 (2H, t, J = 7), 3.89 (3H, s), 4.49 (2H, t, J = 7), 7.21 (1H, dd, J = 7,5), 7.27 (1H, s), 8.17 (1H, s), 8.32 (1H, d, J = 5), 8.41 (1H, s), 8.45 (1H, d, J = 7).

Found M^+ 361
$C_{18}H_{14}N_3O_2F_3$ requires 361

Example 19
6-Chloro-5-methyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline (E19)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (109 mg, 0.67 mmol) in thionyl chloride (5 ml) was stirred for 18 h at room temperature. Excess thionyl chloride was evaporated *in vacuo* and the residue dissolved in dichloromethane was added to a solution of 6-chloro-5-methylindoline (see WO 95/01976) (90 mg, 0.53 mmol) and triethylamine (16 mg, 1.6 mmol) in dichloromethane (5 ml). The mixture was heated at 50°C for 18 h cooled and diluted with dichloromethane (20 ml). The solution was washed with water, then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was triturated repeatedly with diethyl ether to give the title compound as a brown solid (22 mg, 14.%).

^{1}H NMR δ (DMSO): 2.30 (3H, s), 3.15 (2H, t, J = 8Hz), 4.48 (2H, t, J = 8 Hz), 7.20 (1H, m), 7.25 (1H, br s), 8.25 (2H, br s), 8.32 (1H, m), 8.42 (1H, m), HR EI-MS calcd for $C_{17}H_{14}N_3O$ Cl (M^+) 311.0825 found 311.0808.

Example 20
6,7-Dihydro-5-(3-pyrrolo[2,3-b]pyridylcarbonyl)-5H-thieno[2,3-f] indole (E20)

A suspension of pyrrolo[2,3-b]pyridine-3-carboxylic acid (0.5g, 3 mmol) in thionyl chloride (10 ml) was stirred at room temperature for 24 hrs and evaporated to dryness.

T a solution of 6,7-dihydro-5H-thieno[2,3-f]indole (see WO 94/22871) (0.49g, 2.8 mmol) in dichloromethane (10 ml) stirring under argon at room temperature was added a solution of the acid chloride in dichloromethane (5 ml). The solution was stirred for 24

hrs and the precipitate c llected by suction filtration and recrystallised from ethanol/dichloromethane to afford the title compound (0.18g, 20%) as a green powder, m.pt. 273° - 275°C.

^{1}H NMR (250 MHz DMSO) δ: 12.35 (br 1H), 8.55 (s, 1H), 8.40 (dd, 1H), 8.26 (m, 1H), 8.12 (m, 1H), 7.80 (s, 1H), 7.51 (d, 1H), 7.36 (d, 1H), 7.17 (m, 1H), 4.46 (t, 2H), 3.23 (t, 2H).

Pharmacological data

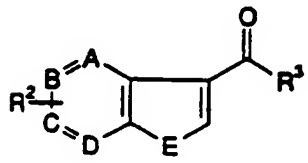
[^{3}H]-mesulergine binding to rat or human 5-HT$_{2C}$ clones expressed in 293 cells in vitro

Compounds can be tested following the procedure outlined in WO 94/04533.

The compounds of examples 1 to 20 have pKi values of 5.2 to 8.3.

CLAIMS:

1. A compound of formula (I) or a salt, solvate or hydrate thereof:



(I)

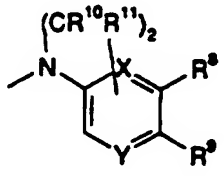
wherein:

A, B, C and D are all carbon atoms or one of A, B, C or D is nitrogen and the others are all carbon;

E is oxygen, sulphur, CH_2 or NR^1 where R^1 is hydrogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylthio, nitro, CF_3, cyano, NR^4R^5, $CONR^4R^5$, CO_2R^6 or OR^7 where R^4, R^5, R^6 and R^7 are as hydrogen or C_{1-6} alkyl; and

R^3 is a group of formula (i)



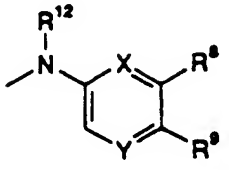
(i)

in which:

X and Y are both nitrogen, one is nitrogen and the other is carbon or a CH group or one is a CH group and the other is carbon or a CH group;

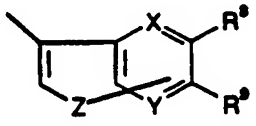
R^8 and R^9 groups are independently C_{1-6} alkyl optionally substituted by one or more halogen atoms, C_{2-6} alkenyl, C_{3-6}cycloalkyloxy, C_{3-6}cycloalkylC_{1-6}alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, C_{1-6} alkylthio, C_{3-6} cycloalkylthio, C_{3-6} cycloalkyl-C_{1-6} alkylthio, C_{1-6}alkoxy, hydroxy, halogen, nitro, CF_3, C_2F_5, OCF_3, SCF_3, SO_2CF_3, SO_2F, formyl, C_{2-6} alkanoyl, cyano, optionally substituted phenyl or thienyl, NR^4R^5, $CONR^4R^5$ or CO_2R^6 where R^4, R^5 and R^6 are as defined for R^1; or R^8 and R^9 form part of an optionally substituted 5-membered carbocyclic or heterocyclic ring; and

R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl;
or R^3 is a group of formula (ii):



(ii)

in which R^8 and R^9 are as defined in formula (i), X and Y are both nitrogen, one is nitrogen and the other is a CH group or X and Y are both CH groups; and
R^{12} is hydrogen or C_{1-6} alkyl,
or R^3 is a group of formula (iii):



in which R^8, R^9, X and Y are as defined for formula (i) and Z is oxygen, sulphur, CH_2 or NR^{13} where R^{13} is hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 in which R^1 and R^2 are hydrogen

3. A compound according to claim 1 or 2 in which R^3 is a group of formula (i).

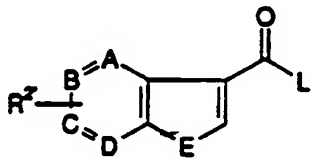
4. A compound according to any one of claims 1 to 3 in which A, B and C are all carbon and D is nitrogen.

5. A compound according to any one of claims 1 to 4 in which E is NH.

6. A compound according to claim 1 which is selected from:
1-(3-Pyrrolo[2,3-b]pyridylcarbonyl)indoline,

5-Nitro-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,
5-Amino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,
5-Dimethylamino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,
5-Diethylamino-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,
N-(1-Methyl-5-indolyl)pyrrolo[2,3-b]pyridine-3-carboxamide,
2,3-Dihydro-6-methyl-3-(3-pyrrolo[2,3-b]pyridylcarbonyl)-1*H*-pyrrolo[3,2-e]indole,
2,3-Dihydro-5-methyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
N-(1-Methyl-5-indolyl)-1-methylpyrrolo[2,3-b]pyridine-3-carboxamide,
2,3-Dihydro-5-methyl-1-(1-methyl-3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-ethyl-1-(1-methyl-3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-pyrrolo[3,2-b]pyridylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-ethyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)pyrrolo[2,3-f]indole
N-(1-Methyl-5-indolyl)pyrrolo[2,3-c]pyridine-3-carboxamide,
2,3-Dihydro-5-ethyl-1-(3-pyrrolo[2,3-c]pyridylcarbonyl)pyrrolo[2,3-f]indole
2,3-Dihydro-5-methyl-1-(3-indolylcarbonyl)pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(1-methyl-3-indolylcarbonyl)pyrrolo[2,3-f]indole
5-Methoxy-6-trifluoromethyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl) indoline
6-Chloro-5-methyl-1-(3-pyrrolo[2,3-b]pyridylcarbonyl)indoline,
6,7-Dihydro-5-(3-pyrrolo[2,3-b]pyridylcarbonyl)-5H-thieno[2,3-f] indole
or pharmaceutically acceptable salts thereof.

7. A process for the preparation of a compound according to claim 1 which comprises:
the coupling of a compound of formula (II):



(II)

with a compound of formula (III):

$$X\text{-}R^{3'} \quad \text{(III)}$$

wherein A, B, C, and D are as defined in formula (I), E is as defined in formula (I) or is a group $NR^{1'}$, L is a leaving group and X is hydrogen or a metal atom, and the variables,

$R^{1'}$, $R^{2'}$ and $R^{3'}$ are R^1, R^2 and R^3 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$ and $R^{3'}$ when other than R^1, R^2 and R^3 respectively to R^1, R^2 and R^3, interconverting R^1, R^2 and R^3 and forming a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 6 for use in therapy.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/03887

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/02 A61K31/44 C07D513/02 //(C07D471/02,221:00, 209:00,209:00),(C07D513/02,333:00,221:00,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO-A-92 05170 (BEECHAM GROUP PLC) 2 April 1992 see the whole document ---	1-9
Y	J.MED.CHEM., vol. 36, 1993 WASHINGTON, pages 1104-1107, FORBES,I.T. ET AL. 'N-(1-Methyl-5-indolyl)-N'-(3-pyridyl)urea Hydrochloride : The first selective 5-HT1c Receptro Antagonist' see the whole document ---	1-9
Y	WO,A,94 18196 (WELLCOME FOUND ;NORMAN MARK HENRY (US); NAVAS FRANK III (US)) 18 August 1994 see the whole document --- -/--	1-9

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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1

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 1996	11.03.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Stellmach, J

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INTERNATIONAL SEARCH REPORT

Inter mal Application No
PCT/EP 95/03887

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Y	WO-A-94 04533 (SMITHKLINE BEECHAM PLC ;FORBES IAN THOMSON (GB); MARTIN ROGER THOM) 3 March 1994 see the whole document	1-9
Y	J.MED.CHEM., vol. 29, 1986 WASHINGTON, pages 2415-2418, FLUDZINSKI,P. ET AL. '2,3-Dialkyl(dimethylamino)indoles: Intersctions with 5HT1,5HT2, and Rat Stomach Fundal Serotonin Receptors' see the whole document	1-9
P,X	WO-A-95 01976 (SMITHKLINE BEECHAM PLC ;HAM PETER (GB); JONES GRAHAM ELGIN (GB); F) 19 January 1995 see the whole document	1-9
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INTERNATIONAL SEARCH REPORT

Inte: nal Application No
PCT/EP 95/03887

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